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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,086	LI ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *11,12 and 14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-10 and 13) in Paper No. 10, received November 4, 2002 is acknowledged. The traversal is on the ground(s) that in the present situation the Examiner has not shown that the search and examination of both groups would entail a serious burden. This is not found persuasive because each group discloses patently distinct groups and the search of one group would not result in the search of the others. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is adhered to.

The requirement is therefore made FINAL.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-23 are pending.

Claims 11, 12 and 14-23, drawn to non-elected inventions are withdrawn from examination.

Claims 1-10 and 13 are examined on the merits.

Priority

3. Applicants submitted corrections to several figures comprising sequences on November 2, 2002 as Paper number 11. Sequences identical to SEQ ID NOS. 1-3 and 5-7 are not found in PCT/US99/14373 (filed June 25, 1999), Provisional Applications number 60/090,906 (filed 6/25/1998) and 60/093,993 (filed July 24, 1998). Thus, for the application of the art to claims 1-10 reciting any of these sequences priority is granted from the instant application's filing date of July 13, 2001. The method of claim 13 is disclosed in all three priority documents. The earliest priority document is U.S. Provisional application number 60/090,906, hence afforded the priority date of June 25, 1998.

Drawings

4. The drawings submitted with the originally filed application are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

The marked up copy of drawings submitted in an effort to correct Figures 1A, 1B-1, 1C, 2B, 2C and 3A reflect changes to the sequences not supported by the priority documents. Additionally there was not corresponding clean copy submitted.

Specification

5. The disclosure is objected to because of the following informalities: the brief description of the figures lacks a separate brief description for Figures 1A-1, 1A-2, 1A-3,

1A-4, 1B-1, 1B-2, 1B-3, 1B-4, 1C-1, 1C-2, 1C-3, 1C-4, 1D-1, 1D-2, 1D-3, 1D-4; Figures 3A-1, 3A-2, 3B-1, 3B-2; and Figures 8A-8E listed on pages 4 and 5.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 and 3-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 1(e) is broadly drawn to a polynucleotide sequence that is at least 90% identical to the polynucleotide sequence that encode polypeptides, SEQ ID NOS: 5-8. And claims 8(a), 9(a) and 10(a) are broadly drawn to any subfragment of SEQ ID NOS: 1-3. The specification while being enabling for the polynucleotides having the nucleic acid sequences of SEQ ID NOS: 1-3, does not reasonably provide enablement for variants that have at least 90% sequence identity to the polynucleotides that encode SEQ ID NOS: 5-8 and subfragments of SEQ ID NO: 1-4. There is no guidance as to how to make these divergent sequences. The products of these 90% sequence identical molecules may encode polypeptides that possess function that may not be commensurate with the functions of the native protein. The 90% sequence identical

polynucleotides may encode polypeptides that may not maintain the activities proposed in the specification. Likewise, subfragments of polynucleotides, SEQ ID NOS: 1-4 may not encode polypeptides capable of acting as enzymes which methylate unmodified CpG sites to establish tissue or gene-specific methylation patterns, such as wild type DNA cytosine methyltransferases. It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as *in vitro* methylation at the C5 position of cytosine in DNA. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art

to make and use the claimed nucleic acids in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which must be made in the nucleic acid sequence of SEQ ID NO: 1-4, which results in nucleic acid sequences with 90% identity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2, 8, 9 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 2 is vague and indefinite in the recitation "under stringent conditions". The metes and bounds are unclear and in the absence of limitations specifying specific stringency conditions.

b. Claims 8 and 9 are vague and indefinite in the recitation "subfragment". It is not clear how many nucleotides are supposed constitute a subfragment. The metes and bounds are unclear.

c. Claim 13 is vague and indefinite in the recitation "effective amount". It is not clear what amount of the *de novo* DNA cytosine methyltransferase polypeptide is deemed effective in order to methylate DNA. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

11. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Okano et al. (Nature Genetics 19:219 and 220, July 19, 1998),as evidenced by Accession number AF068625 (December 6, 1999). Okano as evidenced by Accession #AF068625 discloses Dnmt3a and Dnmnt3b cDNA polynucleotide sequences encoding polypeptides of 908 and 859 amino acids, respectively, see page 219, column 2, second full sentence and attached database sheets. The polynucleotide sequences are at least 20 nucleotides in length and would hybridize to the polynucleotide sequences of claim 1(a), (b) and (e). These polypeptides are the same as Applicants' SEQ ID NO: 5 and SEQ ID NO: 6 and are encoded by polynucleotides that are at least 90% identical to the polynucleotide sequences of claim 1(a) and (b). Both Dnmt3 proteins were expressed using baculovirus expression vectors, see page 220, column 1, first paragraph.

12. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Xie et al. (Gene 236(1): 87-95, 1999),as evidenced by Accession number AF067972 (February 12, 2001). Xie as evidenced by Accession #AF067972 discloses Dnmt3a and Dnmnt3b cDNA polynucleotide sequences encoding polypeptides of 908 and 859 amino acids, respectively, see page 89, column 1, Figure 1 and attached database sheets. The polynucleotide sequences are at least 20 nucleotides in length and would hybridize to the polynucleotide sequences of claim 1(c), (d) and (e). These polypeptides are the same as Applicants' SEQ ID NO: 7 and SEQ ID NO: 8 and are encoded by polynucleotides that are at least 90% identical to the polynucleotide sequences of claim 1(c) and (d). Both Dnmt3 proteins were expressed using baculovirus expression vectors, see page 88, column 1, first paragraph, third sentence.

13. Claims 2 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,183,968 (effective filing date March 27, 1998). U.S. Patent #6,183,968 discloses

a. a polynucleotide sequence at least about 20 nucleotides in length that hybridizes to the polynucleotide sequence of claim 1(a)-(e) under stringent conditions;

b. at least 20 contiguous nucleotides of SEQ ID NO: 2; and

c. a polynucleotide at least about 20 nucleotides in length having a nucleotide sequence complementary to any of the polynucleotide sequences in claim 1(a)-(e), wherein said isolated nucleic acid molecule is not the nucleic acid molecule or

nucleic acid insert identified in the GenBank Accession Reports listed in claims 2, 9 and 10, see attached database sheets.

14. Claims 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AAT21884 of WO9514772 (June 1, 1995). WO9514772 discloses accession #AAT21884 which consists of at least 20 contiguous nucleotides of SEQ ID NO: 1 and SEQ ID NO: 3, as well as a subfragment thereof and a nucleotide sequence complementary to the said nucleotide sequences, see attached database sheet and pages 991 and 992 of WO document.

15. Claim 13 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,492,168 (effective filing date April 22, 1998). U.S. Patent #6,492,168 discloses a method utilizing an expressed novel methyltransferase (M.CviPI) to meythylate GpC *in vitro*, see column 18, lines 31-43 and column 20, lines 60-67. In a reaction mixture containing buffered solutions, cofactors, DNA substrate and M.CviPI the *in vitro de novo* methylation DNA assay was conducted. The DNA was investigated by purifying it from the reaction implementing an ethanol precipitation step.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1 and 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okano et al. (Nature Genetics 19:219 and 220, July 19, 1998), as evidenced by Accession number AF068625 (December 6, 1999) and Xie et al. (Gene 236(1): 87-95, 1999), as evidenced by Accession number AF067972 (February 12, 2001), in view of Ausubel et al. (Current Protocols in Molecular Biology 2, Unit 16.8, see pp.16.8.1-16.11.6). Okano as evidenced by Accession #AF068625 and Xie as evidenced by Accession #A067972 teach the disclosed polynucleotide sequences and these sequences within a baculovirus vector. These references do not teach an expression system capable of producing a *de novo* DNA cytosine methyltransferase polypeptide from said polynucleotide sequence recombinant host cells or recovering the polypeptide from the host cell in proper culture conditions sufficient for production of the polypeptide.

However, Ausubel does teach a baculovirus expression system capable of producing a polypeptide product from the polynucleotide sequences taught in the 102 references and host cells comprising the vector contained polynucleotides specifically in *Spodoptera frugiperda* insect cells. Ausubel also teaches a process for recovering the polypeptides from the culture medium. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the expression system, culture methods and harvesting techniques disclosed by Ausubel for the successful expression of the Dnmt3 polynucleotides. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Ausubel of the great likelihood of obtaining biologically active products from

such methods and host cells due to the baculovirus' efficient promoter strategy and the high infection rate of insect host cells.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER
Alana M. Harris, Ph.D.
January 13, 2003